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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,309	06/06/2001	Masayoshi Mishina	55573	8081

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EXAMINER	
PARAS JR, PETER	

ART UNIT	PAPER NUMBER
1632	13

DATE MAILED: 10/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,309	MISHINA ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendments received on 7/14/03 and 7/24/03 have been entered. Claims 8, 13, and 18 have been amended. Claims 8-22 are pending and are under current consideration.

Drawings

The drawings received on 7/24/03 are accepted.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods to the extent of *in vitro* practice, wherein the germ cell is sperm and the high energy beam is near UV light (330-360nm), does not reasonably provide enablement for all other methods embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to methods of mutating a gene or analyzing the function of a mutated gene of a vertebrate animal comprising treating a germ cell with a psoralen derivative, irradiating the germ cell with a high-energy beam, and subjecting the germ cell to artificial fertilization.

The specification has provided guidance, relevant teachings, and working examples that correlate to practice of the claimed methods *in vitro*, wherein sperm is harvested from zebrafish and treated with 4, 5', 8 trimethylpsoralen and UV light causing mutations in random genes of the zebrafish genome, and wherein treated sperm are then used to fertilize zebrafish oocytes *in vitro* to generate a zebrafish embryo whose genome comprises mutated genes. See pages 16-19 of the specification. The specification has failed to provide guidance for all the other methods embraced by the claims. The specification has failed to fully enable the breadth of the claimed methods. Given the lack of guidance provided by the instant specification it would have required undue experimentation to practice the invention as claimed.

As a first issue, the claims as written embrace both *in vivo* and *in vitro* methods. While, the instant specification has provided guidance for practicing the claimed invention *in vitro*, the instant specification has failed to provide guidance for practicing the claimed invention *in vivo*. The working examples provided by the specification relate to *in vitro* methods of treating sperm with psoralen and UV light, wherein treated sperm are used to fertilize oocytes *in vitro*. The mutagenesis art sets forth that psoralens are capable of mutating DNA upon exposure to near-UV light. See Thomas et al (Mol. Cell. Biol., 1996, 16(5): 2537-2544), which reports "psoralens are a class of heterocyclic aromatic compounds that intercalate into DNA and undergo covalent photocycloaddition with pyrimidines upon exposure to near-UV light (330 to 360nm)". See page 2537. Thomas et al has not commented on other possible mechanisms for

activating the mutagenic capabilities of psoralens; it appears that near UV-light is the only means for activating psoralens. Furthermore, it is well known that light cannot penetrate beyond the skin to affect organs, for example. As the claims read on *in vivo* methods of irradiating a germ cell with a high energy beam, the claims are interpreted to read on exposure of organs, such as the testes and ovaries to a high energy beam. Given, the well-characterized properties of light, particularly near UV light, it appears unpredictable if near UV light can activate the mutagenic properties of psoralens in organs that comprise germ cells, such as testes and ovaries, *in vivo*. In light of the teachings of Thomas et al, it appears that near UV light is the only means for psoralens to mutate DNA. It would have required undue experimentation to practice the full scope of the claims given the lack of guidance provided by the instant specification.

As a second issue, the claims embrace all germ cells. The specification has however, only provided guidance for use of mature sperm cells isolated from zebrafish. Furthermore, the claims require subjecting germ cells to artificial fertilization. As the claims are written, if the germ cell is a mature sperm cell, then it should be artificially fertilized. The specification has not provided guidance that correlates to artificially fertilizing sperm cells; sperm cells are normally known to fertilize oocytes. With regard to claim breadth, all possible germ cells are embraced by the claims. However, it is well-known in the art that certain germ cell types such as preleptotene spermatocytes, zygotene spermatocytes and pachytene spermatocytes have not completed meiosis and are still diploid and do not appear capable of artificially fertilizing an oocyte.

Given the lack of guidance provided by the specification with regard to use of germ cells, other than mature sperm cells, it would have required undue experimentation to practice the full scope of the claims.

Given, the lack of guidance provided by the specification, it would have required undue experimentation to practice the full scope of the invention as claimed.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

Claim 8 is unclear as written. The preamble of the claim is directed to a mutagenesis method of a gene of a vertebrate animal. However, the phrase "a mutagenesis method of a gene" has no clear meaning, as it appears to mean that the mutagenesis method is a property of the gene. Appropriate correction is required. The following claim language is suggested: "A method of mutating a gene". Claims 9-12 depend from claim 8.

Claims 8, 13, and 18 are indefinite as written. The claims require subjecting an irradiated germ cell to artificial fertilization to induce mutagenesis of a gene in an embryo. The claims are indefinite as written because it is not known how artificial fertilization can induce mutagenesis of a gene in an embryo. Neither the specification nor any art of record has defined how artificial fertilization induces mutagenesis of a gene. Given the teachings of the specification it appears that genes can be mutated by treating germ cells with psoralen and UV light. Appropriate correction is required. Claims 9-12, 14-17, and 19-22 depend from claims 8, 13, and 18 respectively.

Claim 18 is indefinite as written. The claim is directed to a method for analyzing the function of a gene of a vertebrate animal. The method steps result in examination of the correlation between the mutated gene and a mutant phenotype. The claim is indefinite as written because the claim does not specify how analyzing the function of a gene of a vertebrate animal relates to examination of the correlation between the mutated gene and a mutant phenotype. Claims 19-22 depend from claim 18.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakrabarti et al (Genetics, 1983, 103: 109-123), Grunwald et al #1 (Genet. Res., 1991, 59: 93-101) and Grunwald et al #2 (Genet. Res., 1991, 59: 103-116) taken with Thomas et al (Mol. Cell. Biol., 1996, 16(5): 2537-2544).

The claims are directed to methods of mutating a gene or analyzing the function of a mutated gene of a vertebrate animal comprising treating a germ cell with a psoralen derivative, irradiating the germ cell with a high-energy beam, and subjecting the germ cell to artificial fertilization.

Chakrabarti et al teach a method of mutating genes in the zebrafish genome comprising providing sperm collected from a zebrafish, irradiating the collected sperm with γ-rays, and fertilizing isolated zebrafish oocytes with the irradiated sperm, to produce a zebrafish embryo whose genome comprises mutated genes. See page 110. In particular, Chakrabarti et al correlated the effects of mutating the gol-1 gene with a mutant phenotype; the mutant gol-1 zebrafish comprise both pigmented and unpigmented patches in the retina of the eye. See pages 114-115. Grunwald et al #1 teach similar methods to those of Chakrabarti with the main difference being use of UV light irradiation as a mutagen instead of γ-ray irradiation. See page 94. Grunwald et al #1 as

Chakrabarti correlated the effects of mutating the gol-1 gene with a mutant phenotype; the mutant gol-1 zebrafish comprise both pigmented and unpigmented patches in the retina of the eye. See pages 95-96. Grunwald et al #2 teach similar methods to those of Chakrabarti and Grunwald #1 with the main difference being use of ethylnitrosourea (ENU) as a mutagen rather than UV light or γ-ray irradiation. See pages 104-105. Grunwald et al #2 as Chakrabarti and Grunwald #1 correlated the effects of mutating the gol-1 gene with a mutant phenotype; the mutant gol-1 zebrafish comprise both pigmented and unpigmented patches in the retina of the eye. See pages 110-112. The collective teachings of Chakrabarti, Grunwald #1, and Grunwald #2 set forth the use of different mutagens for inducing germline mutations in zebrafish for the purpose of analyzing gene function in zebrafish.

The collective teachings of Chakrabarti, Grunwald #1, and Grunwald #2 differ from the claimed invention, as they do not teach use of a psoralen derivative, particularly 4, 5', 8-trimethylpsoralen, as a mutagen.

However at the time the claimed invention was made, use of psoralen derivatives as mutagens was within the purview of the ordinary artisan. In particular, Thomas et al teach that psoralens are mutagenic compounds of vegetable origin that are a class of heterocyclic aromatic compounds that intercalate into DNA and undergo covalent photocycloaddition with pyrimidines upon exposure to near UV light (330-360nm). See page 2537. Thomas et al specifically teach use of 4, 5', 8-trimethylpsoralen and near UV light to induce mutations in DNA found in human cell extracts. See throughout the entire

document. Thomas et al teach that mutations induced by psoralen/near-UV treatment are mainly T:A—C:G transitions, transversions at C:G base pairs, and deletions of single A:T base pairs. See the abstract and page 2541. The teachings of Thomas suggest psoralens, particularly 4, 5', 8-trimethylpsoralen, represent a difference class of mutagens capable of inducing different types of mutations from other known mutagens.

Accordingly, in view of the routine state of the art as represented by Thomas et al, it would have been obvious to modify the methods of Chakrabarti, Grunwald #1, and Grunwald #2 by substituting mutagens such as γ-ray irradiation, UV irradiation and ENU with 4, 5', 8-trimethylpsoralen with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as it was an art-recognized goal to mutate genes of zebrafish for analyzing gene function in zebrafish as discussed by Chakrabarti, Grunwald #1, and Grunwald #2.

Thus, the claimed invention, as a whole, was clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Official Fax Center number is (703) 872-9306.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.

Art Unit 1632

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